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=> FILE USPAT

FILE 'USPAT' ENTERED AT 16:49:14 ON 02 APR 1998

  * * * * * * * * * * * * * * * * * * * * * * * * * * * * * * * * *
  *                  W E L C O M E   T O   T H E                  *
  *          U. S.   P A T E N T   T E X T   F I L E              *
  * * * * * * * * * * * * * * * * * * * * * * * * * * * * * * * * *


=> D HIS FULL


     (FILE 'USPAT' ENTERED AT 16:33:52 ON 02 APR 1998)
                SET LINELENGTH 78
L1           964 SEA 514/81,86/CCLST OR 544/243,244/CCLST OR 546/23/CCLST
L2            49 SEA ?OXYCARBONYLOXYMETHYLOXY? OR ?OXYCARBONYLOXYMETHOXY?
L3             0 SEA ?AMINOCARBONYLOXYMETHYLOXY? OR ?AMINOCARBONYLOXYMETHOXY?

L4             4 SEA ?CARBOALKOXYMETHYLOXY? OR ?CARBOALKOXYMETHOXY?
L5            70 SEA ?CARBOMETHOXYMETHYLOXY? OR ?CARBOMETHOXYMETHOXY?
L6            44 SEA ?CARBOETHOXYMETHYLOXY? OR ?CARBOETHOXYMETHOXY?
L7             5 SEA ?CARBOPROPOXYMETHYLOXY? OR ?CARBOPROPOXYMETHOXY?
L8             0 SEA ?CARBOISOPROPOXYMETHYLOXY? OR ?CARBOISOPROPOXYMETHOXY?
L9             0 SEA ?CARBOARYLOXYMETHYLOXY? OR ?CARBOARYLOXYMETHOXY?
L10            0 SEA ?CARBOPHENOXYMETHYLOXY? OR ?CARBOPHENOXYMETHOXY?
L11          155 SEA (L2 OR L3 OR L4 OR L5 OR L6 OR L7 OR L8 OR L9 OR L10)
L12            1 SEA L1 AND L11
L13         1734 SEA PRODRUG OR BIOREVERSIBLE(W)PROTECTING(W)GROUP
                E BIOREVERS
L14          133 SEA (BIOREVERSIBILITY/BI OR BIOREVERSIBLE/BI OR BIOREVERSIBLY
                /BI)
L15           42 SEA L1 AND (L13 OR L14)
                DELETE SAVED/A
                DELETE US0893982601/Q
L16           43 SEA L12 OR L15

=> D L12

1.  5,463,071, Oct. 31, 1995, 5-membered heterocyclic compounds, processes
for preparing them and pharmaceutical compositions containing these
compounds; Frank Himmelsbach, et al., 548/251; 544/122, 232, 238, 243;
546/21, 22, 193, 209, 210, 256, 268.4, 272.7, 274.1, 275.1; 548/111, 254
[IMAGE AVAILABLE]

=> SAVE L16 US0890074601/A

ANSWER SET 'L16' HAS BEEN SAVED AS 'US0890074601/A'

=> LOG Y

U.S. Patent & Trademark Office LOGOFF AT 16:52:02 ON 02 APR 1998
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FILE 'CAPLUS' ENTERED AT 11:52:13 ON 03 APR 1998

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L2	543171	S	ED>970724
L3	1	S	L1 AND L2

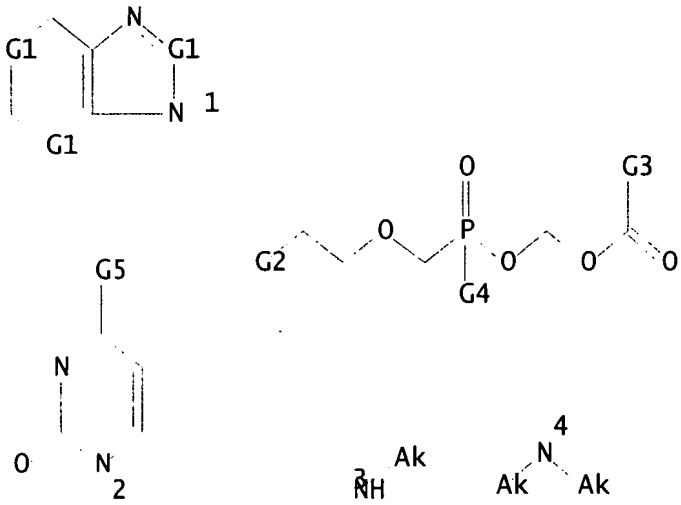
=> FILE REGISTRY CAPLUS

FILE 'REGISTRY' ENTERED AT 13:43:23 ON 01 APR 1998
USE IS SUBJECT TO THE TERMS OF YOUR STN CUSTOMER AGREEMENT.
PLEASE SEE "HELP USAGETERMS" FOR DETAILS.

FILE 'CAPLUS' ENTERED AT 13:43:23 ON 01 APR 1998
USE IS SUBJECT TO THE TERMS OF YOUR STN CUSTOMER AGREEMENT.
PLEASE SEE "HELP USAGETERMS" FOR DETAILS.

=> D QUE L4

L1 STR



G1 N,C
G2 [@1],[@2]
G3 O,N
G4 H,O,N
G5 NH2,[@3],[@4]

Structure attributes must be viewed using STN Express query preparation.
L3 12 SEA FILE=REGISTRY SSS FUL L1
L4 2 SEA FILE=CAPLUS L3

=> D L4 TOTAL CBIB IABS HITSTR

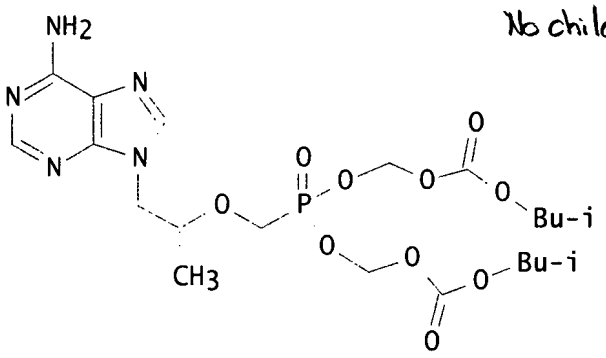
L4 ANSWER 1 OF 2 CAPLUS COPYRIGHT 1998 ACS
1998:102883 Document No. 128:140970 Preparation of phosphonomethoxy acyclic nucleotide analogs as antiviral agents. Arimilli, Murty N.; Cundy, Kenneth C.; Dougherty, Joseph P.; Kim, Choung U.; Oliyai, Reza; Stella, Valentino J. (Gilead Sciences, Inc., USA). PCT Int.

Appl. WO 9804569 A1 980205, 74 pp. DESIGNATED STATES: W: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, GH, HU, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, UZ, VN, YU, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM; RW: AT, BE, BF, BJ, CF, CG, CH, CI, CM, DE, DK, ES, FI, FR, GA, GB, GR, IE, IT, LU, MC, ML, MR, NE, NL, PT, SE, SN, TD, TG. (English). CODEN: PIXXD2. APPLICATION: WO 97-US13244 970725. PRIORITY: US 96-686838 960726; US 96-22708 960726.

GRAPHIC IMAGE:

ABN (8/18/97) No child

Prov. App (this app priority)



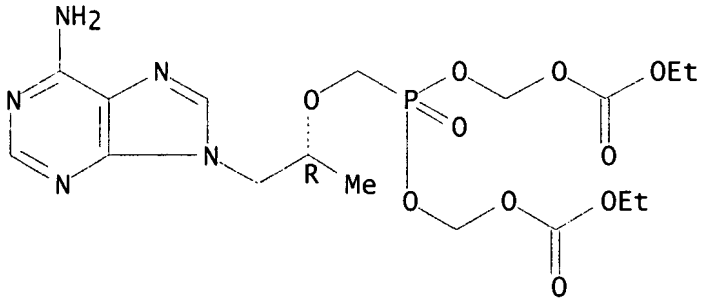
I

ABSTRACT:
Compds. are provided that comprise esters of antiviral phosphonomethoxy nucleotide analogs with carbonates and/or carbamates having the structure B-OC(R2)2OC(O)X(R)n, wherein R2 independently is H, C1-C12 alkyl, aryl, alkenyl, alkynyl, alkyenylaryl, alkynylaryl, alkaryl, arylalkynyl, arylalkenyl or arylalkyl which is (un)substituted with halo, azido, nitro or OR3 in which R3 is C1-C12 alkyl; X is N or O; R is independently H, C1-C12 alkyl, aryl, alkenyl, alkynyl, alkyenylaryl, alkynylaryl, alkaryl, arylalkynyl, arylalkenyl or arylalkyl which is (un)substituted with halo, azido, nitro, -O-, -N=, -NR4, -N(R4)2- or OR3, R4 independently is -H or C1-C8 alkyl, provided that at least one R is not H; and n is 1 or 2, with the proviso that when n is 2 and X is N, (a) two R groups can be taken together to form a carbocycle or oxygen-contg. heterocycle, or (b) one R addnl. can be OR3. The compds. are useful as intermediates for the prepn. of antiviral compds. or oligonucleotides, or are useful for administration directly to patients for antiviral therapy or prophylaxis. Embodiments are particularly useful when administered orally. Thus , acyclic nucleotide I was prepd. and showed anti-HIV activity (IC50 < 0.001 .mu.M).

IT **201340-95-6P**
RL: BAC (Biological activity or effector, except adverse); RCT (Reactant); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(prepn. of phosphonomethoxy acyclic nucleotide analogs as antiviral agents)
RN 201340-95-6 CAPLUS
CN 2,4,6,8-Tetraoxa-5-phosphanonanedioic acid, 5-[[2-(6-amino-9H-purin-

9-yl)-1-methylethoxy]methyl]-, diethyl ester, 5-oxide, (R)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.

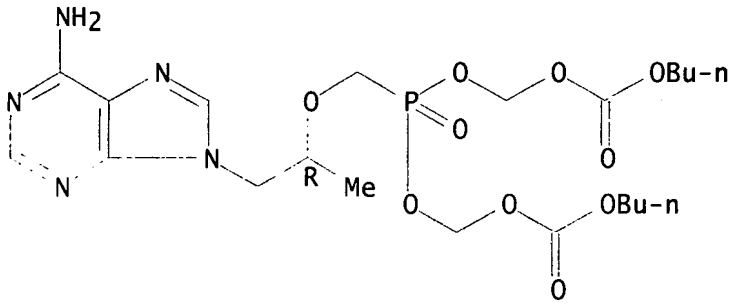


IT **201340-97-8P 201340-99-0P 201341-01-7P 201341-03-9P 201341-05-1P 201341-07-3P 201341-09-5P 201341-11-9P 202138-50-9P 202138-51-0P 202138-54-3P**
RL: BAC (Biological activity or effector, except adverse); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(prepn. of phosphonomethoxy acyclic nucleotide analogs as antiviral agents)

RN 201340-97-8 CAPLUS

CN 2,4,6,8-Tetraoxa-5-phosphanonanedioic acid, 5-[[2-(6-amino-9H-purin-9-yl)-1-methylethoxy]methyl]-, dibutyl ester, 5-oxide, (R)- (9CI) (CA INDEX NAME)

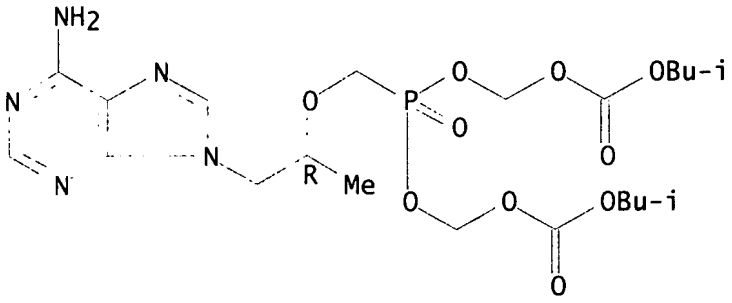
Absolute stereochemistry.



RN 201340-99-0 CAPLUS

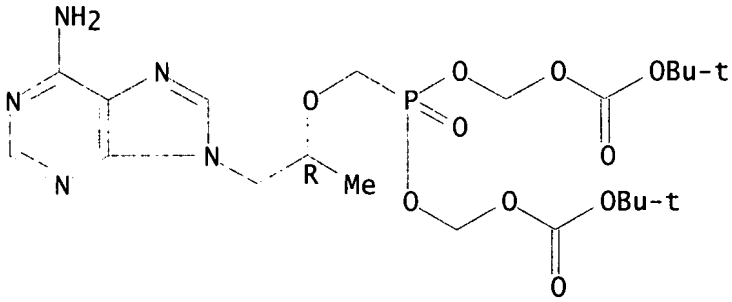
CN 2,4,6,8-Tetraoxa-5-phosphanonanedioic acid, 5-[[2-(6-amino-9H-purin-9-yl)-1-methylethoxy]methyl]-, bis(2-methylpropyl) ester, 5-oxide, (R)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



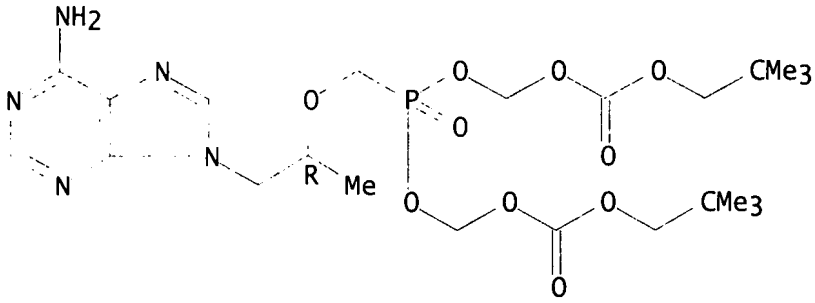
RN 201341-01-7 CAPLUS
CN 2,4,6,8-Tetraoxa-5-phosphanonanedioic acid, 5-[[2-(6-amino-9H-purin-9-yl)-1-methylethoxy]methyl]-, bis(1,1-dimethylethyl) ester, 5-oxide, (R)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



RN 201341-03-9 CAPLUS
CN 2,4,6,8-Tetraoxa-5-phosphanonanedioic acid, 5-[[2-(6-amino-9H-purin-9-yl)-1-methylethoxy]methyl]-, bis(2,2-dimethylpropyl) ester, 5-oxide, (R)- (9CI) (CA INDEX NAME)

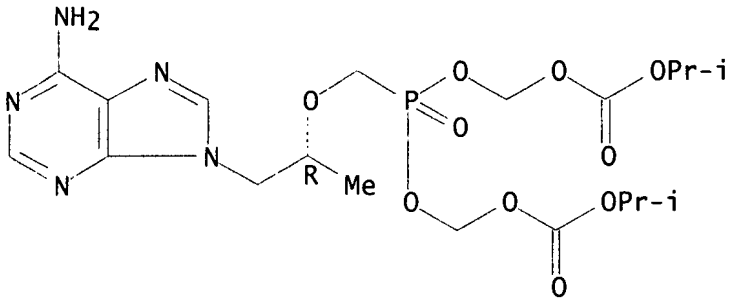
Absolute stereochemistry.



RN 201341-05-1 CAPLUS
CN 2,4,6,8-Tetraoxa-5-phosphanonanedioic acid, 5-[[2-(6-amino-9H-purin-9-yl)-1-methylethoxy]methyl]-, bis(1-methylethyl) ester, 5-oxide,

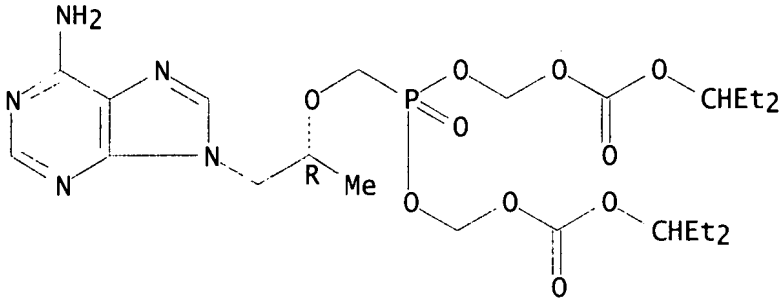
(R)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



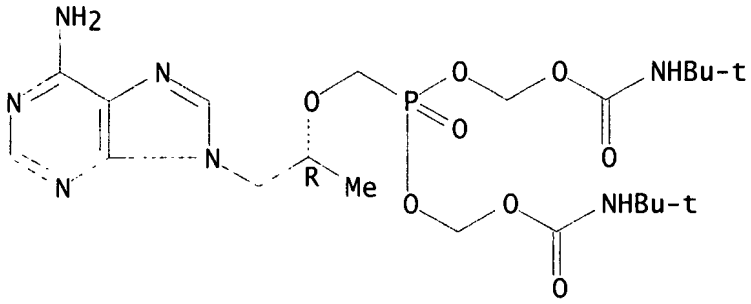
RN 201341-07-3 CAPLUS
CN 2,4,6,8-Tetraoxa-5-phosphanonanedioic acid, 5-[[2-(6-amino-9H-purin-9-yl)-1-methylethoxy]methyl]-, bis(1-ethylpropyl) ester, 5-oxide, (R)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



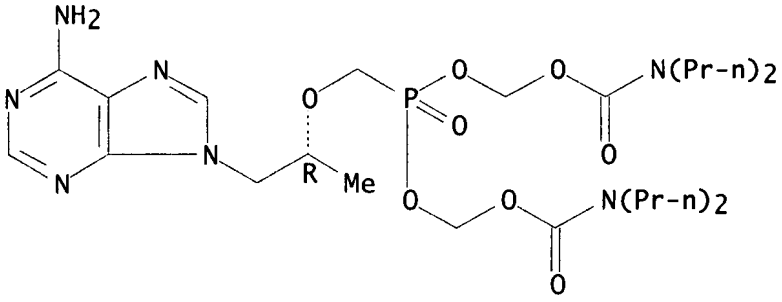
RN 201341-09-5 CAPLUS
CN Carbamic acid, (1,1-dimethylethyl)-, [[[2-(6-amino-9H-purin-9-yl)-1-methylethoxy]methyl]phosphinylidene]bis(oxymethylene) ester, (R)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



RN 201341-11-9 CAPLUS
CN Carbamic acid, dipropyl-, [[[2-(6-amino-9H-purin-9-yl)-1-methylethoxy]methyl]phosphinylidene]bis(oxymethylene) ester, (R)-(9CI) (CA INDEX NAME)

Absolute stereochemistry.

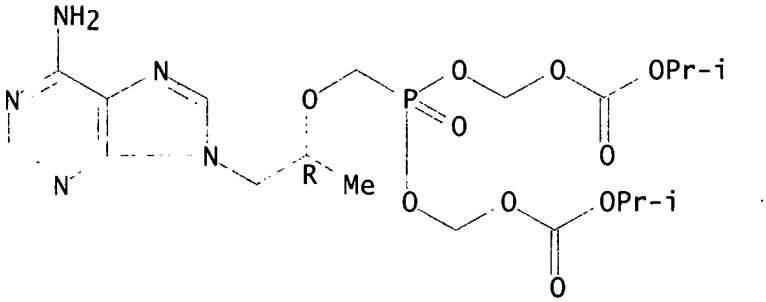


RN 202138-50-9 CAPLUS
CN 2,4,6,8-Tetraoxa-5-phosphanonanedioic acid, 5-[[2-(6-amino-9H-purin-9-yl)-1-methylethoxy]methyl]-, bis(1-methylethyl) ester, 5-oxide, (R)-, (E)-2-butenedioate (1:1) (9CI) (CA INDEX NAME)

CM 1

CRN 201341-05-1
CMF C19 H30 N5 O10 P

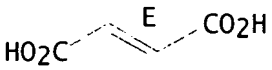
Absolute stereochemistry.



CM 2

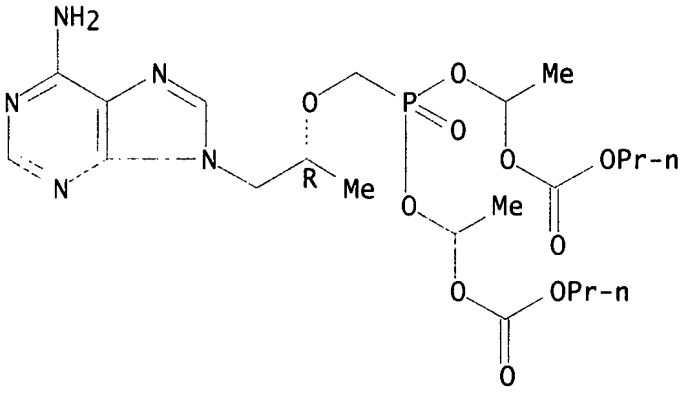
CRN 110-17-8
CMF C4 H4 O4
CDES 2:E

Double bond geometry as shown.



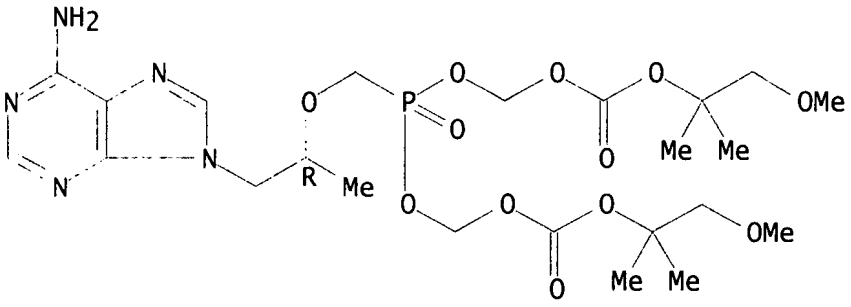
RN 202138-51-0 CAPLUS
CN Carbonic acid, [[[2-(6-amino-9H-purin-9-yl)-1-methylethoxy]methyl]phosphinylidene]bis(oxyethylidene) dipropyl ester, stereoisomer (9CI) (CA INDEX NAME)

Absolute stereochemistry.



RN 202138-54-3 CAPLUS
CN 2,4,6,8-Tetraoxa-5-phosphanonanedioic acid, 5-[[2-(6-amino-9H-purin-9-yl)-1-methylethoxy]methyl]-, bis(2-methoxy-1,1-dimethylethyl) ester, 5-oxide, (R)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



L4 ANSWER 2 OF 2 CAPLUS COPYRIGHT 1998 ACS
1997:762860 Document No. 128:97300 Synthesis, in vitro biological evaluation and oral bioavailability of 9-[2-(phosphonomethoxy)propyl]adenine (PMPA) prodrugs. Arimilli, M. N.; Kim, C. U.; Dougherty, J.; Mulato, A.; Oliyai, R.; Shaw, J. P.; Cundy, K. C.; Bischofberger, N. (Gilead Sci., Foster City, CA, 94404, USA). Antiviral Chem. Chemother., 8(6), 557-564 (English) 1997. CODEN: ACCHEH. ISSN: 0956-3202. Publisher: International

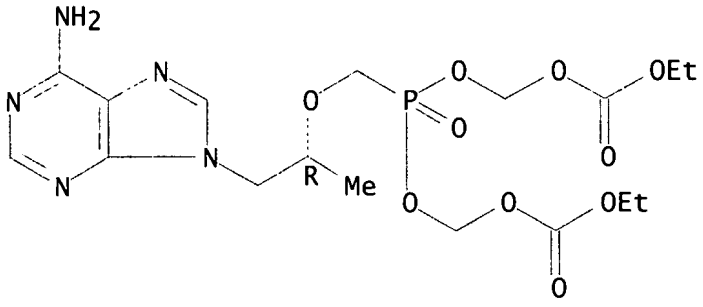
Medical Press.

ABSTRACT:
Potentially orally bioavailable prodrugs of the antiretroviral agent 9-[2-(phosphonomethoxy)propyl]adenine (PMPA) were evaluated. Alkyl Me carbamates were synthesized by alkylation of PMPA with the corresponding alkyl chloromethyl carbonate and N-alkyl chloromethyl carbamate reagents. The prodrugs were evaluated for in vitro antiviral activity in addn. to chem. and enzymic stability. The inhibition of human immunodeficiency virus type 1 (HIV-1) strain IIIB replication of MT-2 cells by the carbonate prodrugs was found to be 2.5-500-fold increased compared to PMPA. The alkyl Me carbonates, except t-Bu Me carbonate, had reasonable chem. stability at pH 2.2 and 7.4, but were rapidly converted to the corresponding monoester of PMPA in the presence of dog plasma. The alkyl Me carbamate prodrugs such a N-t-Bu Me carbamate were found to have high stability in vitro. Based on its chem. stability and good oral bioavailability, bis(POC)PMPA (iso-Pr methylcarbonate) was chosen as a clin. candidate.

IT **201340-95-6P 201340-97-8P 201340-99-0P**
201341-01-7P 201341-03-9P 201341-05-1P
201341-07-3P 201341-09-5P 201341-11-9P
RL: BAC (Biological activity or effector, except adverse); PRP (Properties); SPN (Synthetic preparation); BIOL (Biological study); PREP (Preparation)
(prepn., antiretroviral activity, and oral bioavailability of 9-[2-(phosphonomethoxy)propyl]adenine prodrugs)

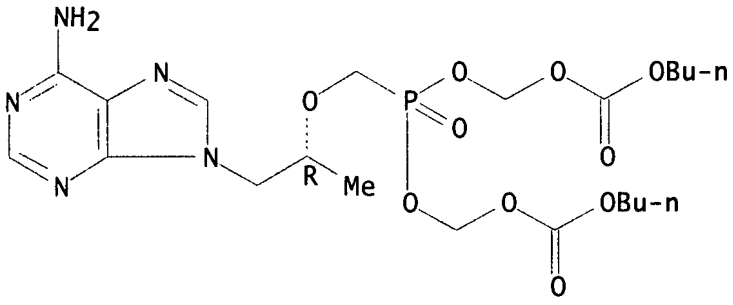
RN 201340-95-6 CAPLUS
CN 2,4,6,8-Tetraoxa-5-phosphanonanedioic acid, 5-[[2-(6-amino-9H-purin-9-yl)-1-methylethoxy]methyl]-, diethyl ester, 5-oxide, (R)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



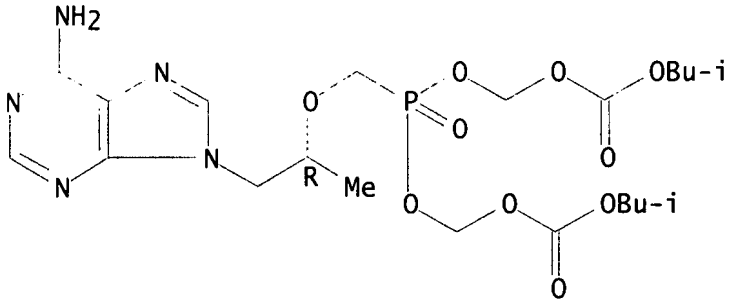
RN 201340-97-8 CAPLUS
CN 2,4,6,8-Tetraoxa-5-phosphanonanedioic acid, 5-[[2-(6-amino-9H-purin-9-yl)-1-methylethoxy]methyl]-, dibutyl ester, 5-oxide, (R)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



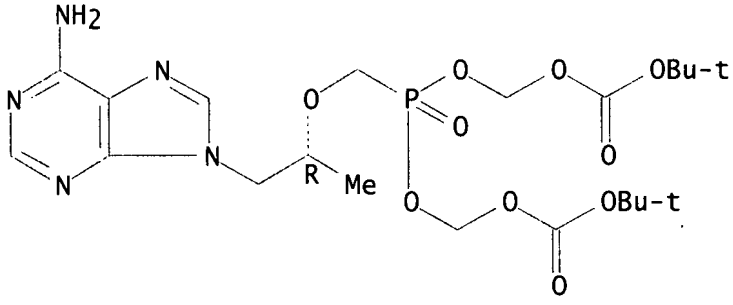
RN 201340-99-0 CAPLUS
CN 2,4,6,8-Tetraoxa-5-phosphanonanedioic acid, 5-[[2-(6-amino-9H-purin-9-yl)-1-methylethoxy]methyl]-, bis(2-methylpropyl) ester, 5-oxide, (R)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



RN 201341-01-7 CAPLUS
CN 2,4,6,8-Tetraoxa-5-phosphanonanedioic acid, 5-[[2-(6-amino-9H-purin-9-yl)-1-methylethoxy]methyl]-, bis(1,1-dimethylethyl) ester, 5-oxide, (R)- (9CI) (CA INDEX NAME)

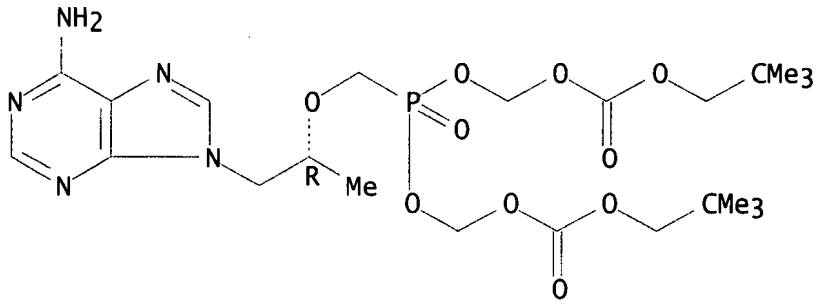
Absolute stereochemistry.



RN 201341-03-9 CAPLUS
CN 2,4,6,8-Tetraoxa-5-phosphanonanedioic acid, 5-[[2-(6-amino-9H-purin-9-yl)-1-methylethoxy]methyl]-, bis(2,2-dimethylpropyl) ester,

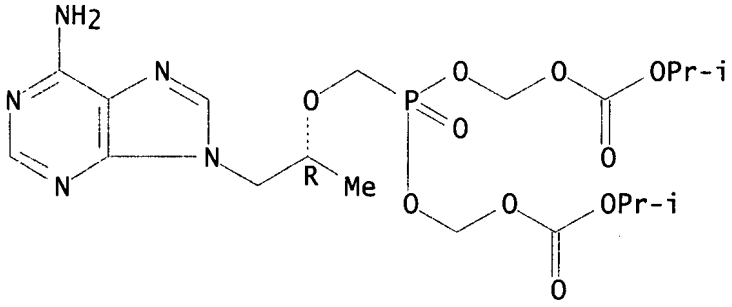
5-oxide, (R)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



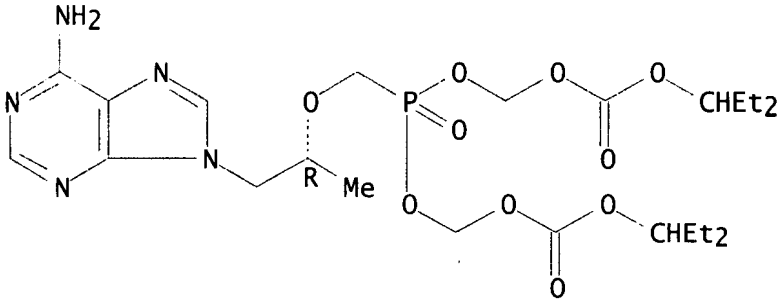
RN 201341-05-1 CAPLUS
CN 2,4,6,8-Tetraoxa-5-phosphanonanedioic acid, 5-[[2-(6-amino-9H-purin-9-yl)-1-methylethoxy]methyl]-, bis(1-methylethyl) ester, 5-oxide, (R)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



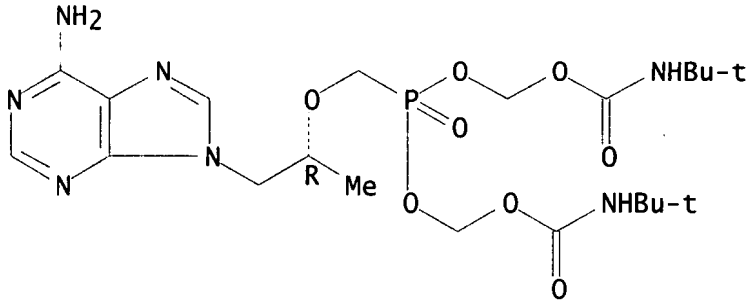
RN 201341-07-3 CAPLUS
CN 2,4,6,8-Tetraoxa-5-phosphanonanedioic acid, 5-[[2-(6-amino-9H-purin-9-yl)-1-methylethoxy]methyl]-, bis(1-ethylpropyl) ester, 5-oxide, (R)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



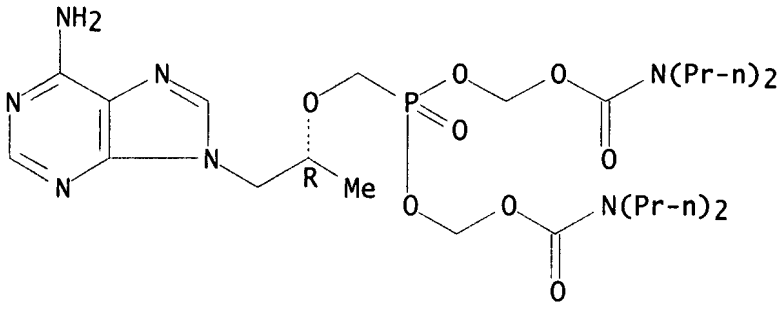
RN 201341-09-5 CAPLUS
CN Carbamic acid, (1,1-dimethylethyl)-, [[[2-(6-amino-9H-purin-9-yl)-1-methylethoxy]methyl]phosphinylidene]bis(oxymethylene) ester, (R)-(9CI) (CA INDEX NAME)

Absolute stereochemistry.



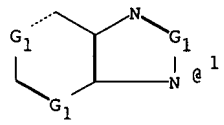
RN 201341-11-9 CAPLUS
CN Carbamic acid, dipropyl-, [[[2-(6-amino-9H-purin-9-yl)-1-methylethoxy]methyl]phosphinylidene]bis(oxymethylene) ester, (R)-(9CI) (CA INDEX NAME)

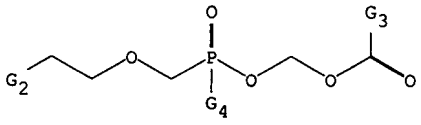
Absolute stereochemistry.

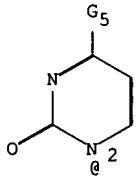


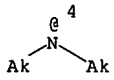
=> LOG H

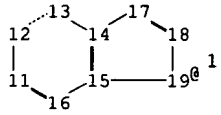
SESSION WILL BE HELD FOR 60 MINUTES
STN INTERNATIONAL SESSION SUSPENDED AT 13:53:12 ON 01 APR 1998

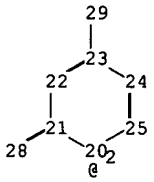


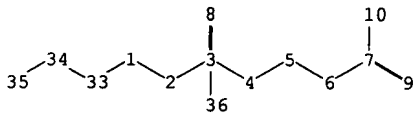


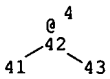












chain nodes :
4 5 6 7 8 9 10 28 29 34 35 39 40 41 42 43
ring nodes :
11 12 13 14 15 16 17 18 19 20 21 22 23 24 25
ring/chain nodes :
1 2 3 33 36
chain bonds :
3-4 3-8 4-5 5-6 6-7 7-9 7-10 21-28 23-29 33-34 34-35 39-40
41-42 42-43
ring/chain bonds :
1-2 1-33 2-3 3-36
ring bonds :
11-12 11-16 12-13 13-14 14-15 14-17 15-16 15-19 17-18 18-19
20-21 20-25 21-22 22-23 23-24 24-25
exact/norm bonds :
3-8 3-36 7-9 7-10 11-12 11-16 12-13 13-14 14-15 14-17 15-16
15-19 17-18 18-19 20-21 20-25 21-22 21-28 22-23 23-24 23-29
24-25
exact bonds :
1-2 1-33 2-3 3-4 4-5 5-6 6-7 33-34 34-35 39-40 41-42 42-43

G1:N,C

G2:[*1],[*2]

G3:O,N

G4:H,O,N

G5:NH2,[*3],[*4]

Connectivity :
40:1ERC 41:1ERC 43:1ERC
Match level :
1:Atom 2:Atom 3:Atom 4:Atom 5:Atom 6:Atom 7:Atom 8:Atom 9:Atom
10:Atom 11:Atom 12:Atom 13:Atom 14:Atom 15:Atom 16:Atom 17:Atom
18:Atom 19:Atom 20:Atom 21:Atom 22:Atom 23:Atom 24:Atom 25:Atom
28:Atom 29:Atom 33:Atom 34:Atom 35:Atom 36:Atom 39:Atom 40:Atom
41:Atom 42:Atom 43:Atom
Element Count :
Node 40: Limited
C,C3

Node 41: Limited
C,C3

Node 43: Limited
C,C3